REMARKS

The title of the application has been amended by replacing "Regulating" with "Inhibiting." Support for this amendment can be found in Example 8 starting on page 46, line 25 and corresponding Figure 15 (demonstrating that expression of a receptor containing a substitution mutation at Ser^{601} inhibits the survival of CTL-EN cells cultured under low serum conditions) and Example 13 starting on page 55, line 1 (demonstrating that cultured cells expressing either beta-chain mutant S601G or beta chain mutant RSL→ AAA exhibit apoptosis in the presence of IL-3 -- *see* page 56, line 14 to page 57, line 2) of the substitute specification filed February 2, 2007.

Claims 73, 75, and 79 have been amended and cancel claims 74 and 78, without prejudice. Support for the amendment to claim 73 can be found on page 35, lines 19-32 (describing the making of expression plasmids containing a substitution mutation at Ser^{601}), page 36, line 25 to page 37, line 3 (describing the transfection of the plasmids containing the mutation into cells), Example 8 starting on page 46, line 25 and corresponding Figure 15 (demonstrating that expression of a receptor containing a substitution mutation at Ser^{601} inhibits the survival of CTL-EN cells cultured under low serum conditions), Example 10 starting on page 49, lines 6 (teaching the use of beta-chain mutant S601G), and Example 13 starting on page 55, line 1 (demonstrating that cultured cells expressing either beta-chain mutant S601G or beta chain mutant RSL→ AAA exhibit apoptosis in the presence of IL-3 -- *see* page 56, line 14 to page 57, line 2) of the substitute specification filed February 2, 2007. The amendments to claims 75 and 79 are made to correct for antecedent basis in light of the amendment to claim 73. No new matter has been added. Claims 73, 75-77, and 79 are pending and at issue.

Objection to the Specification

The Examiner has objected to the title of application, "Method of Regulating Hematopoietic Cell Survival," because the pending claims are limited to methods of inhibiting cell survival. As suggested by the Examiner, Applicants have amended the title of the application to read "Method of Inhibiting Hematopoietic Cell Survival." Therefore, Applicants respectfully request withdrawal of this objection.

Enablement Rejection

Claims 73-79 remain rejected under 35 U.S.C. §112, first paragraph, as not enabled because, according to the Examiner, the specification does not enable (1) mutations of the binding motif other than those exemplified and (2) a method of inhibiting hematopoietic cells survival *in vivo*. The Examiner, however, states that a method of decreasing hematopoietic cell survival *in vitro* comprising mutating the sequence HSRSLP (residues 598-603) of SEQ ID NO: 1 to EFAAAA is enabled. *See* page 4 of the Office Action.

The Examiner contends that the single mutation of the binding motif described in the specification and its function is not predictive of the vast number of other mutations as claimed and, therefore, undue experimentation would have been required to test these mutants to determine whether each mutant inhibits cell survival as claimed.

Claim 73 has been amended to recite that the binding motif includes a substitution mutation at Ser^{601}. Undue experimentation would not have been required to determine whether each mutant receptor covered by the amended claims inhibits cell survival in light of the 8 factors described in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Concerning the first and second factors of breadth of the claims and nature of the invention, the claims have been narrowed to set forth that the mutations are limited to receptors with a substitution mutation at Ser^{601}. The third, fourth, and fifth factors relate to the state of the prior art, the level of one of ordinary skill in the art, and the level of predictability in the art, respectively, and generally, relate to what was known at the time of the invention. The level of skill and knowledge was high at the time of the invention because methods to make cells containing the mutant receptor as well as methods to assay these cells for their survival were well known. The sixth, seventh, and eighth factors encompass what is disclosed in the application and, specifically, are the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, respectively. Regarding the claimed invention, specification describes and provides several examples of the claimed invention. In particular, Applicants respectfully point out that contrary to the Examiner's statements, receptors with a beta-

chain mutation S601G and beta chain mutation RSL→AAA also exhibit apoptosis (*see* page 56, line 14 to page 57, line 2 of the substitute specification filed February 2, 2007). In sum, knowledge in the art and the specification provide an abundance of information such that only routine and undue experimentation is required to make and use the claimed invention.

The Examiner contends that no evidence has been presented showing that *in vitro* activity is predictive of *in vivo* (*e.g.*, in an organism) activity and that one skilled in the art could not use *in vitro* results to predict results *in vivo*. Additionally, the Examiner argues that the specification provides no methods or examples of the administration of hematopoietic cells expressing the mutant receptor or the creation of transgenic animals expressing the mutant receptor.

It is not beyond the skilled addressee to predict or extrapolate from *in vitro* data to an *in vivo* situation. The invention is based on the discovery that expression of a GM-CSF/IL-3/IL-5 receptor, in which there is a substitution mutation at serine residue 601 of the beta chain of the receptor, inhibits hematopoietic cell survival. Methods to introduce the mutated sequence encoding the receptor are known in the art both in an *in vitro* and in an *in vivo* setting because the amended claims set forth a small genus of methods each requiring that the receptor contains a substitution mutation at Ser^{601} and, thus, the *in vitro* results of the specification can be applied *in vivo*.

Thus, since one of ordinary skill in the art would understand that *in vitro* data is predictive of *in vivo* application and no undue experimentation is required to make and use the claimed invention as described above, the claimed invention is fully enabled and Applicants respectfully request withdrawal of the enablement rejection.

Indefiniteness Rejection

The indefiniteness rejection under 35 U.S.C. §112, second paragraph, of claims 73-79 has been maintained because, according to the Examiner, the claims fail to recite an essential step. According to the Examiner, the body of claim 73 does not set forth that the survival of the hematopoietic cell is regulated and, therefore, does not indicate that the goal of the preamble of "inhibiting hematopoietic cell survival" is achieved. The Examiner further contends that the

claimed method is missing a step setting forth that the mutated protein is expressed in a cell to decrease cell survival.

In accordance with the Examiner's suggestion, Applicants have amended claim 73 to recite the step of expressing a mutant receptor in a cell such that the survival of the cell is inhibited. Applicants respectfully request withdrawal of this indefiniteness rejection.

Anticipation Rejection

The Examiner has maintained the rejection of claims 73-79 under 35 U.S.C. §102(b) as anticipated by Smith *et al.* (*EMBO* 1997, 16:451-464). The Examiner contends that the residues disclosed by Smith correspond to the residues included in SEQ ID NO: 1 of the instant application. According to the Examiner, Smith teaches a truncated β-chain that includes a deletion of residues 598-603 of the wild type receptor and that this truncated β-chain does not support the growth of transfected CTLL2 cells. The Examiner asserts that (1) the claims do not include a limitation that the length of SEQ ID NO:1 is largely maintained and (2) the claims encompass mutations that are deletions of one or more of the ^{598}HSRSLP^{603} residues. Thus, according to the Examiner, the truncated β-chain of Smith includes a deletion of residues 598-603 of the receptor as claimed and, therefore, anticipates the claimed method of mutating the ^{598}HSRSLP^{603} sequence of the receptor.

Claims 73 has been amended to recite a mutant with a substitution mutation at Ser^{601}. In other words, the length of the receptor is substantially conserved. In contrast, Smith teaches the deletion of entire segments of the β-chain ranging in size from 114 to 436 amino acid residues. Thus, Smith neither teaches nor suggests the claimed invention. Applicants, therefore, respectfully request withdrawal of this anticipation rejection.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the proposed amendment be entered, and that all pending claims be

allowed and the case passed to issue. Since the amendments address the Examiner's rejections and would place the claims in condition for allowance, or at least in better form for consideration on appeal, entry is proper. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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